REMARKS

By this amendment, claims 1-3, 6, 8, 9, 16-18, and 23 are revised and arguments are made in support of the patentability of the invention. Currently, claims 1-24 are before the Examiner for consideration on their merits and claims 25-30 are withdrawn from consideration.

First, claim 6 is revised so that it corresponds with claim 5 and the objection in this regard is now overcome.

Second, the claims are revised to remove the use of ranges associated with "preferably" and ""for example" and the rejection based on 35 USC 112, second paragraph is overcome.

In review, the Examiner rejects claim 1 under 35 USC 103 based on the combination of three references, the article to Bazzi (Bazzi), United States Published Patent Application No. 2004/0075083 to Li et al. (Li), and United States Patent No. 6,099,964 to Baumann et al. (Baumann). In making this rejection, the Examiner cites Bazzi as teaching a luminescent hybrid nanoparticle having rare earths.

The Examiner admits that Bazzi does not teach the claimed polysiloxane coating, the coating thickness, or the ligand grafted to the coating.

Li is cited to teach siloxane coated nanoparticles, with the coating having functional groups. With the teachings of Li, the Examiner concludes that it would be obvious to employ the functional group-containing siloxane coating of Li with the nanoparticles of Bazzi.

Admitting that the claimed thickness is not disclosed, the Examiner relies on Baumann to allege that it would be obvious to employ the claimed thickness for the

coating on the Bazzi nanoparticles. Baumann is cited to demonstrate that a siloxane coating of 1-100 nm is known and therefore, it would be obvious to use such a coating thickness.

The Examiner also indicates that the combination is proper since a reasonable expectation of success would exist in the eyes of the artisan to produce a 5 nm nanoparticle.

Applicants respectfully traverse the rejection on the grounds that the Examiner does not have the proper reasons for modifying Bazzi and, as such, a prima facie case of obviousness is not established. The traverse is set out below under the headings of the INVENTION and ARGUMENTS.

INVENTION

One purpose of the invention is to propose new hybrid probe nanoparticles for biological labelling in in vitro and in vivo applications. These probes have to be sufficiently small for presenting a more important "stealth" or molecularity and an increased stability in front of the aqueous exterior medium aggressions, see page 4 lines 2-4, of the instant patent application. The new biological probes according to the invention with their controlled size and composition offer different possibilities regarding their functionality and can be produced according to a simple and easily industrializable process.

For this purpose, claim 1 of the present patent application proposes:

Hybrid nanoparticles containing:

- a nanosphere, of mean diameter included in the range from 2 to 9 nm, of which at least 90% by weight consists of Ln_2O_3 where Ln represents a rare earth optionally doped with a rare earth and an actinide, or a mixture of rare

earths, or a rare earth and actinide mixture, in which at least 50% of the metal ions are rare earth ions,

- a coating around the nanosphere chiefly consisting of functionalized polysiloxane, having a mean thickness included in the range form 0.5 to 10 nm, preferably greater than 2nm and no more than 10 nm,
- and at least one biological ligand grafted by covalent bonding to the polysiloxane coating.

So the claimed nanoparticles are characterized by:

a) their core defined by its particularly small size and its composition that, among others, confers to the nanoparticles luminescent properties, indeed magnetic ones, theses properties being a function of the rare earth ions present in the nanoparticles,

b) the coating which, due to its composition and its thickness, ensures the protection of the nanospheres when they are dispersed in an aqueous medium and avoid intensity loss generally observed when the nanospheres are dispersed in water, see page 12, lines 9-13,

c) the presence of biological ligand grafted to the surface which offers different possibilities for biological applications, for instance as a probe.

For in vivo biological applications, for instance for those mentioned page 14, lines 19-20 of the instant patent application, the nanoparticles according to the invention which combine a very small size and an important stability, are compatible with intravenous injection and renal elimination.

Such applications were confirmed by the inventions in two publications:

« Hybrid gadolinium oxide nanoparticles: multimodal contrast agents for in vivo imaging » Journal of American Chemical Society 2007; and

« Hybrid gadolinium oxide nanoparticles combining imaging and therapy » Journal of Materials Chemistry 2009.

Moreover, it can be understood that these two publications, which relate to the applications of the claimed nanoparticles, were cited a high number of times by the

scientific community (around 200 accrued citations).

Furthermore, the coating with its particular composition and thickness protects the luminescent properties of the Ln_2O_3 core and authorizes the energy transfer from the nanospheres. That is to say, the UV excitation is absorbed by the coating of polysiloxane and transferred to the spherical core. As a result, an increases in luminescent is obtained, see page 9, lines 8-11, of the patent application.

So, the claimed nanoparticles, with their essential characteristics, that is:

- the composition and the particularly small size of the core nanosphere,
- the presence of a protective coating made of polysiloxane which represents, in every cases, at least 25% of the final volume of the nanoparticle and can reach 99,9% of the final volume of the nanoparticle, and
- the surface functionalization,

are endowed with a combination of original characteristics that are essential for in vivo applications and that were not described nor suggested in the prior art.

ARGUMENTS

One question of patentability turns on whether the Examiner has properly modified the teachings of Bazzi so as to allege that the invention is obvious. Applicants do not dispute that the nanoparticles of Bazzi correspond to the nanospheres of the claimed nanoparticles. Nevertheless, there is nothing in Li or in Bauman that would lead the man skilled in the art to modify Bazzi in order to obtain the claimed invention.

Li deals with Europium-containing fluorescent nanoparticles. Their core is constituted by an aluminium oxide framework having a europium activator, a magnesium, calcium, strontium, or barium energy reservoir, and at least one co-activator selected from the group consisting of scandium, yttrium, and certain

lanthanide elements. The nanoparticles may be optionally coated with a silane coating containing reactive functional groups that allow for attachment of the nanoparticle to a desired biological or chemical target molecule.

In Li, it is indicated that the size of the nanoparticles is in the range of 1-1000 nm preferably 5-200 nm, and more preferably 10-100 nm (see paragraph [0021] page 2).

The size and the composition (aluminium oxide framework) of the nanoparticles are quite different from those of the claimed nanoparticles and Bazzi. According to the invention, the coating has to protect the core but the obtaining of the coating must not increase the size of the obtained nanoparticles.

In Li, the composition of the particles is different from the composition of the nanospheres of the invention or Bazzi. In fact and according to the invention, the composition surface of the inventive nanospheres modifies the physic-chemical conditions of the sol-gel technique used for coating, see Example 1 for sol gel coating formation. As a result, the nucleation processes and the homogeneous or non-homogeneous character of the coating obtained by such a process can be achieved.

Applicants are not merely claiming to put a siloxane coating on the particles of Bazzi. Instead, claim 1 requires an extremely small size nanosphere as well as an extremely thin coating so that the size of the particles are not drastically increased.

Applicants submit that just because Li teaches a siloxane-coated fluorescent nanoparticle, this does not mean that it is obvious to specify the size of the nanosphere and attendant siloxane coating. Even if it were obvious, doing so provides significant advantages as explained above.

In fact, Applicants contend that it was not even possible using Li to obtain so small of particles with a polysiloxane coating as in the invention. Li is not even concerned with the thickness aspect of the coating since there is no description whatsoever of the thickness. Why select the claimed thickness? Li does not realize the importance of minimizing the increase in size of the nanospheres when producing the siloxane coating. That is, the coating, due to its composition and thickness ensures protection of the nanospheres even when they are dispersed in an aqueous medium. The intensity loss generally observed when the nanospheres are dispersed in water is thus avoided. Thus, the nanoparticles of very small size and stability can be used in applications that the particles of Bazzi could not, e.g., intravenous injection and renal elimination.

In taking the position that one of skill in the art would use the coating of Li on the particles of Bazzi, the Examiner overlooks the intricacies required when coating nanoparticles and the fact that the particle of Li being coated is not the same as that of Bazzi. Claim 1 requires the nanosphere to be at least 90% by weight Ln_2O_3, whereas Li has a nanosphere that has a substantial amount of aluminium oxide. This means that the particles of Li cannot be considered to be the same as Bazzi or that which is claimed. So, how does the coating of Li get applied to a particle like that of Bazzi when the two particles are not the least similar?

Applicants submit that the Examiner has committed error in the rejection by failing to take into account that the particles of Li and that of Bazzi are not the same so that the routineer also has to conclude that the coating of Li can be easily applied in such a way that the claimed thickness of coating can be achieved. Applicants contend

that it would not be obvious to apply the process described by Li to nanospheres of Ln_2O_3 according to the invention. This is because the non specific nucleation and non cross linking between nanospheres that occurs when coating a Ln_2O_3 nanosphere is essential for keeping a small size when the nanospheres are coated. Indeed, the sol-gel processes, which are used for the coating in the examples are very sensitive to all these parameters.

Additionally, in Li, the coating is obtained with a heat treatment (see claim 11 and example 3 "heated in a microwave oven"). In the case of the invention, for biological applications, for insertion of organic fluorophore and in order to avoid agglomerations, such heating cannot be used.

It is also important to underline that the interest of the coating used in the invention is not limited to the incorporation of biological ligands. Other purposes among others, which are not mentioned in Li, are its protective effect and the obtaining of a controlled porosity (that allows a water ratio useful for IRM applications, for instance).

To conclude, the mere fact that Li teaches a siloxane coating on a nanoparticle does not by itself mean that the particles of Bazzi can be coated according to the claimed parameters. Again, since Li says nothing about the coating thickness nor teaches a process similar to that employed by the invention, it is factually unsupported to conclude that the coating and coating thickness can be derived from the teachings of Li.

Baumann does not remedy the failings in the rejection based on Li. First, the particles described in Baumann are even more removed from the nanoparticles of the

claimed invention than the particles of Li.

Baumann teaches organopolysiloxane particles consisting of a single molecule, which are cross-linked, contain metal atoms in the zero valent oxidation state, the metal atoms in each case being in intermetallic interaction with at least one further metal atom in the zero valent oxidation state, have an average diameter of 5 to 200nm and are soluble to the extent of at least 0.1% by weight in at least one organic solvent.

The particles are qualified as mesoscopic and the size given in the examples (see example 1) are higher than 10nm. In this case also, the physic-chemical conditions (composition and size of the particles, lack of functionalization for the binding of biological ligands) are very different with respect to the features of the invention.

Baumann do not describe the combination of a nanosphere, of mean diameter included in the range from 2 to 9 nm with a coating around the nanosphere having a mean thickness included in the range form 0.5 to 10 nm, which corresponds a thick coating, comparing to the dimension of the core.

So, it was not predictable, starting from Bazzi that such a coating can be made on a nanosphere of Ln_2O_3. Additionally, the problems of fluorescence preservation, protection to exterior attacks and functionalization with biological ligand are not mentioned in Baumann.

In citing Baumann to address the failure of Bazzi and Li to teach the claimed thickness, the Examiner is merely identifying a shell thickness that happens to appear in the prior art and then baldly concluding that this thickness can be applied to the Bazzi nanoparticle as modified according to the teachings of Li. The problem with the Examiner's reasoning is that the Examiner cannot separate the purpose of the coating

of Baumann from its thickness. Put another way, the Examiner is merely plucking the thickness of the siloxane shell of Baumann to use in the rejection, while ignoring the fact that the siloxane shell of Baumann is produced in a context which is completely and totally unrelated to either Bazzi or Li.

As stated above, Baumann relates to organopolysiloxane particles, with or without metal atoms, that include a siloxane shell. Applicants submit that one of skill in the art, knowing of Baumann would have no reason to employ the shell parameters of Baumann for the siloxane coating suggested by Li? The process of making the shell of Baumann is completely unrelated to the siloxane coating of Li. Therefore, how is such a shell thickness, which is designed to cover an organopolysiloxane molecule, to be used or even obtained in an aluminium oxide core nanoparticle taught by Li.? The Examiner is violating the mandate stated in KSR that just because something is known in the prior art does not mean that something can be used to formulate an obviousness position. This is the error committed in relying on Baumann to allege that one of skill in the art would control the thickness of the siloxane coating on the nanoparticle of Bazzi to that thickness suggested by Baumann.

Finally, Applicants contend that the double patenting rejection is improper since the applied application is prior art against the instant application, see its effective filing date and compare it with the instant application's effective filing date. Further, it is not co-owned by the Assignee of this application so that a Terminal Disclaimer could not be properly filed. Thus, this rejection should be withdrawn.

In summary, Applicants submit that the Examiner has not established a prima facie case of obviousness because the proper reasoning is not used to modify Bazzi

using either Li or Baumann. Therefore, claim 1 is patentable over this prior art. Since claim 1 is patentable, its dependent claims are also in condition for allowance.

Accordingly, the Examiner is requested to examine this application and pass all pending claims onto issuance.

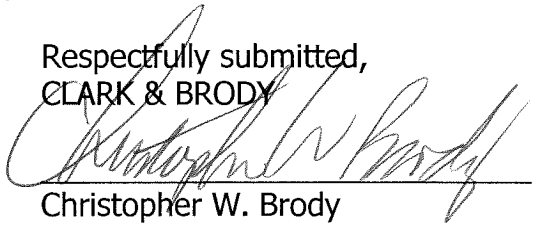
If the Examiner believes that an interview would be helpful in expediting the allowance of this application, the Examiner is requested to telephone the undersigned at 202-835-1753.

The above constitutes a complete response to all issues raised in the outstanding Office Action.

Again, reconsideration and allowance of this application is respectfully requested.

Applicants submit that no fee is due in connection with this filing. However, any fee deficiency should be charged to Deposit Account No. 50-1088.

Respectfully submitted,
CLARK & BRODY



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